The Role of HPV Testing in Clinical Guidelines for Cervical Cancer Prevention

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HEALTH DEPARTMENT

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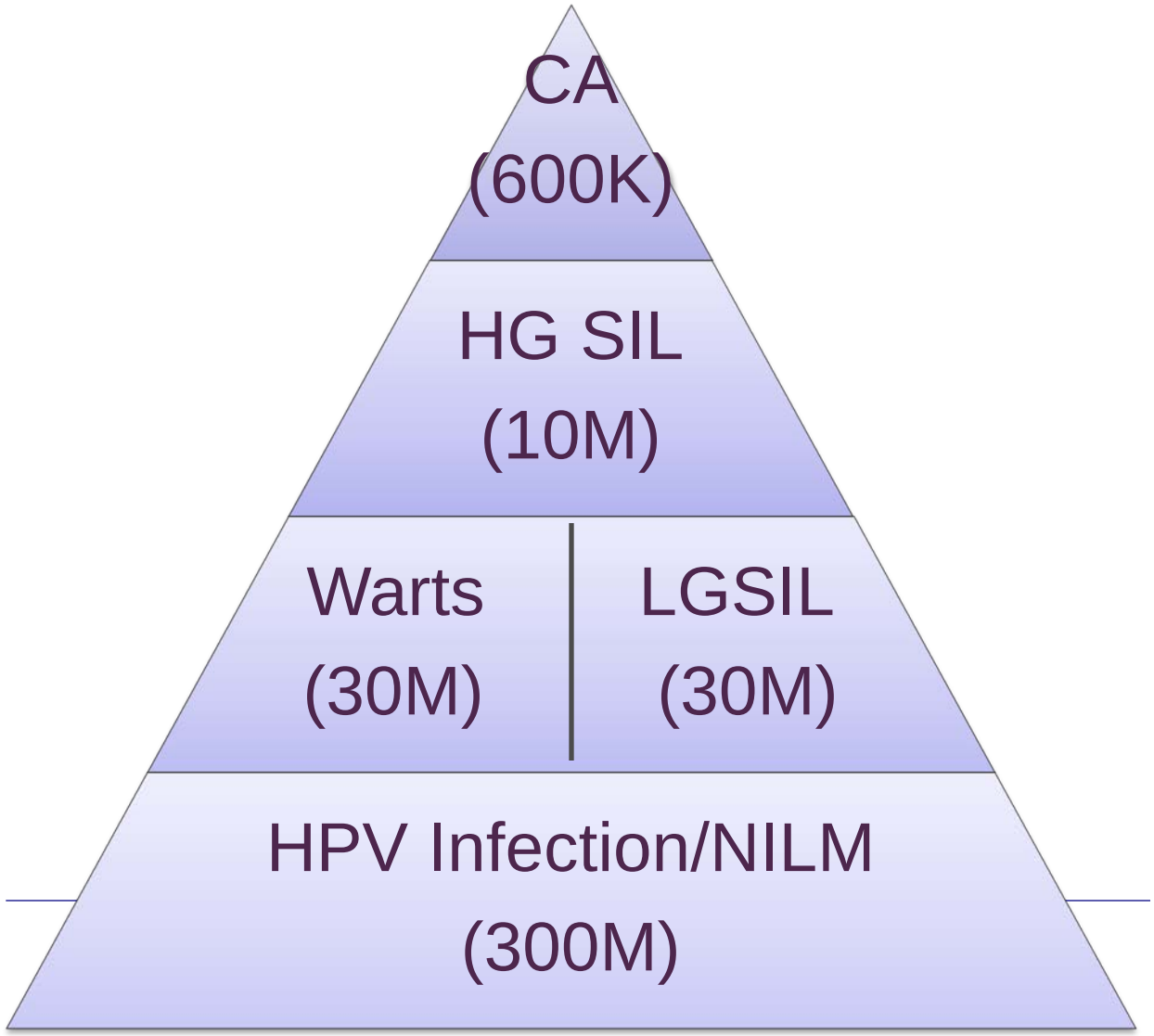
Objectives

- Review current understanding of epidemiology and natural history HPV infection and cervical cancer precursor
- Discuss the evolution of screening guidelines and their application to the public health setting
- Will NOT review/comment on primary screening data HPV test under review

Global Burden of HPV Related Disease



Cancer Risk

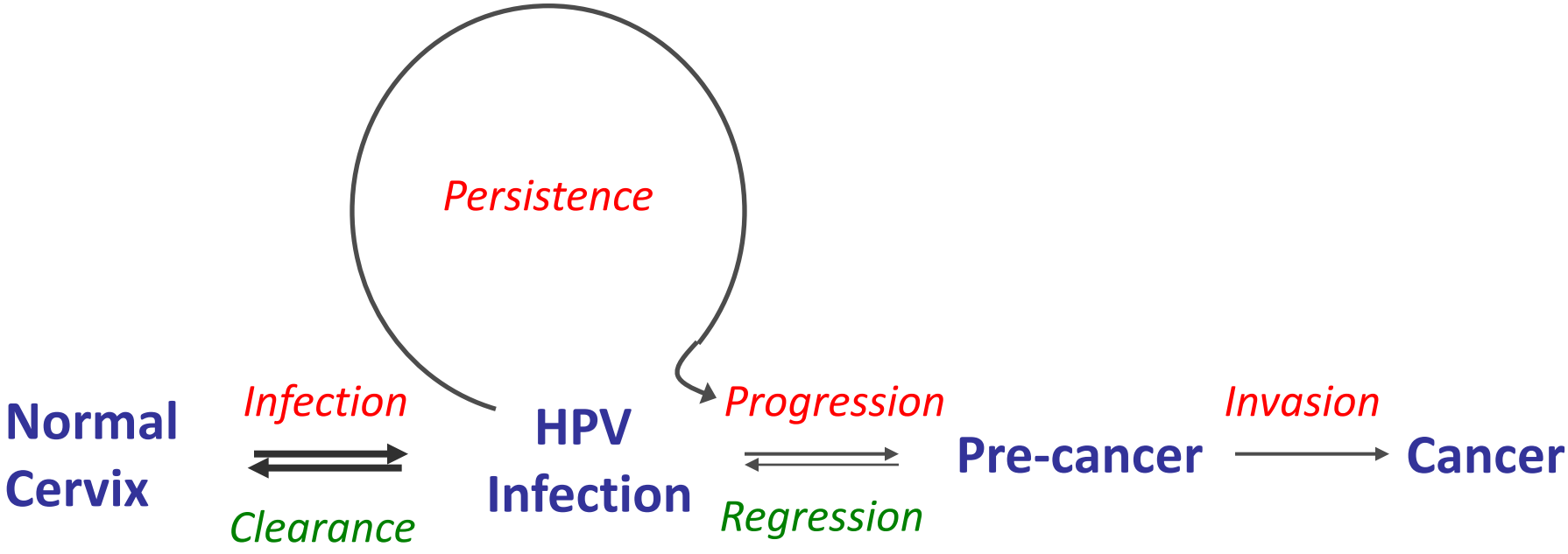
1/1

1/20

1/60

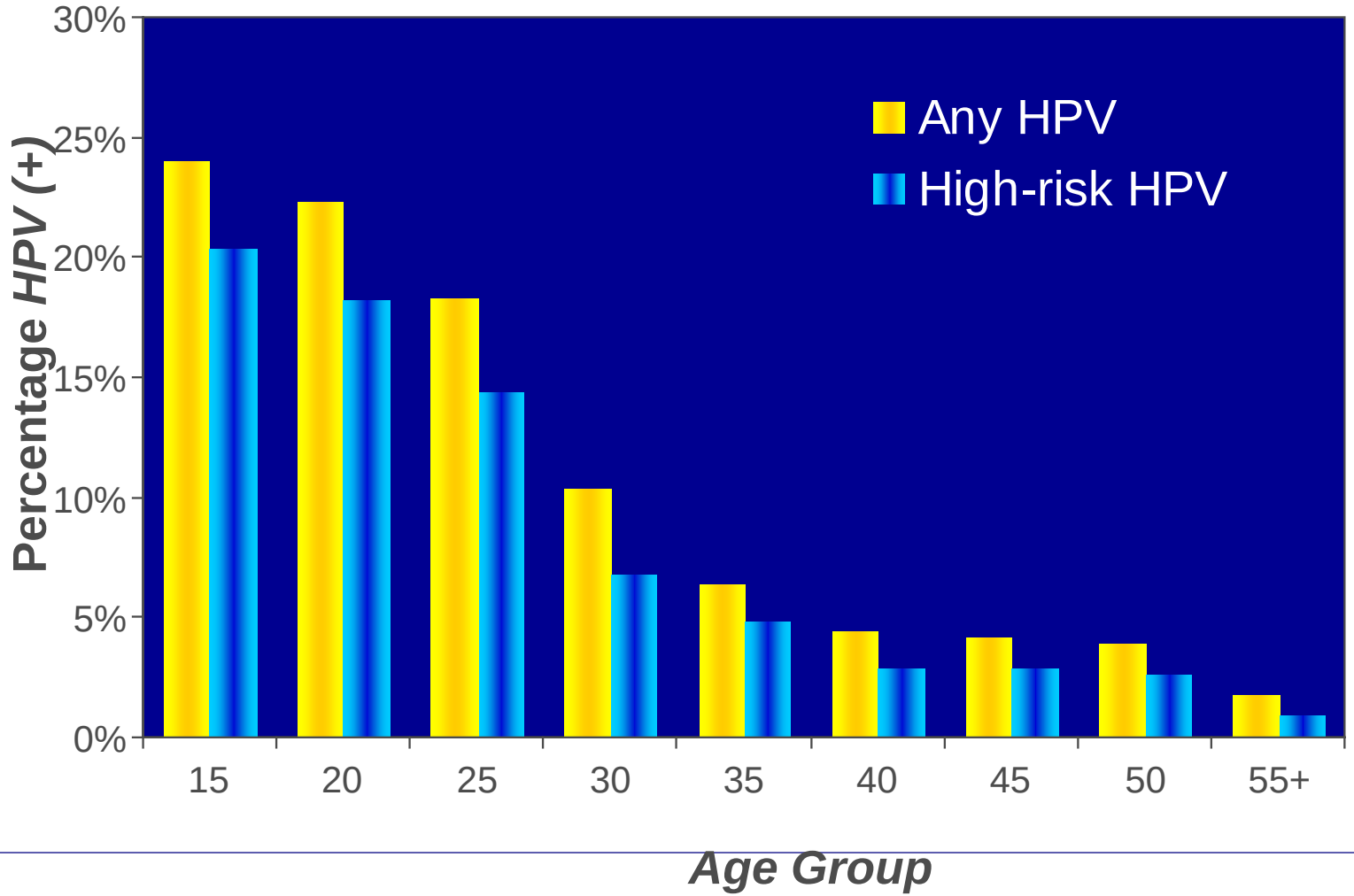
1/600

Natural History of HPV Infection & Cervical Cancer



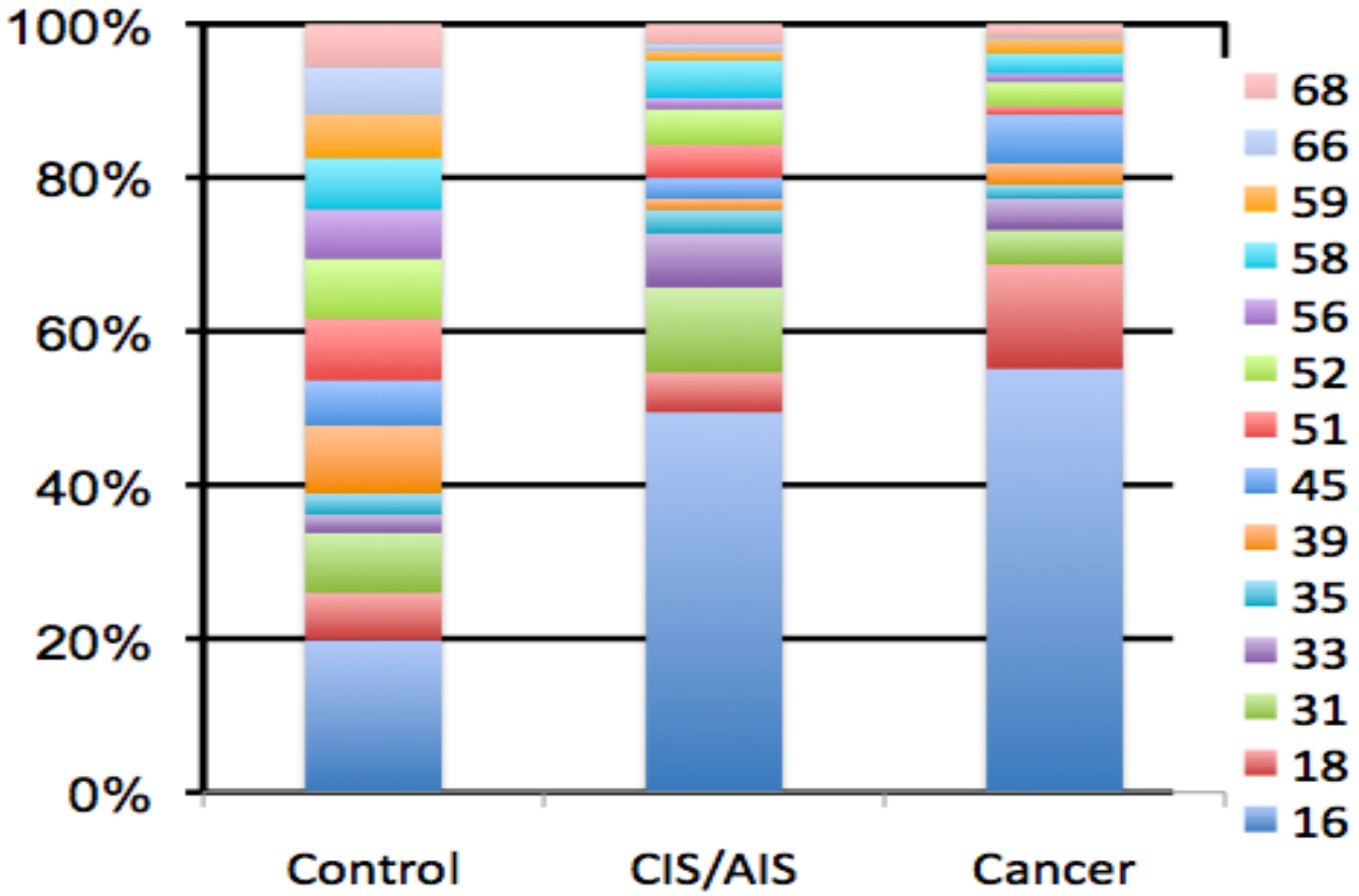
Courtesy of M. Schiffman

HPV Positivity by Age



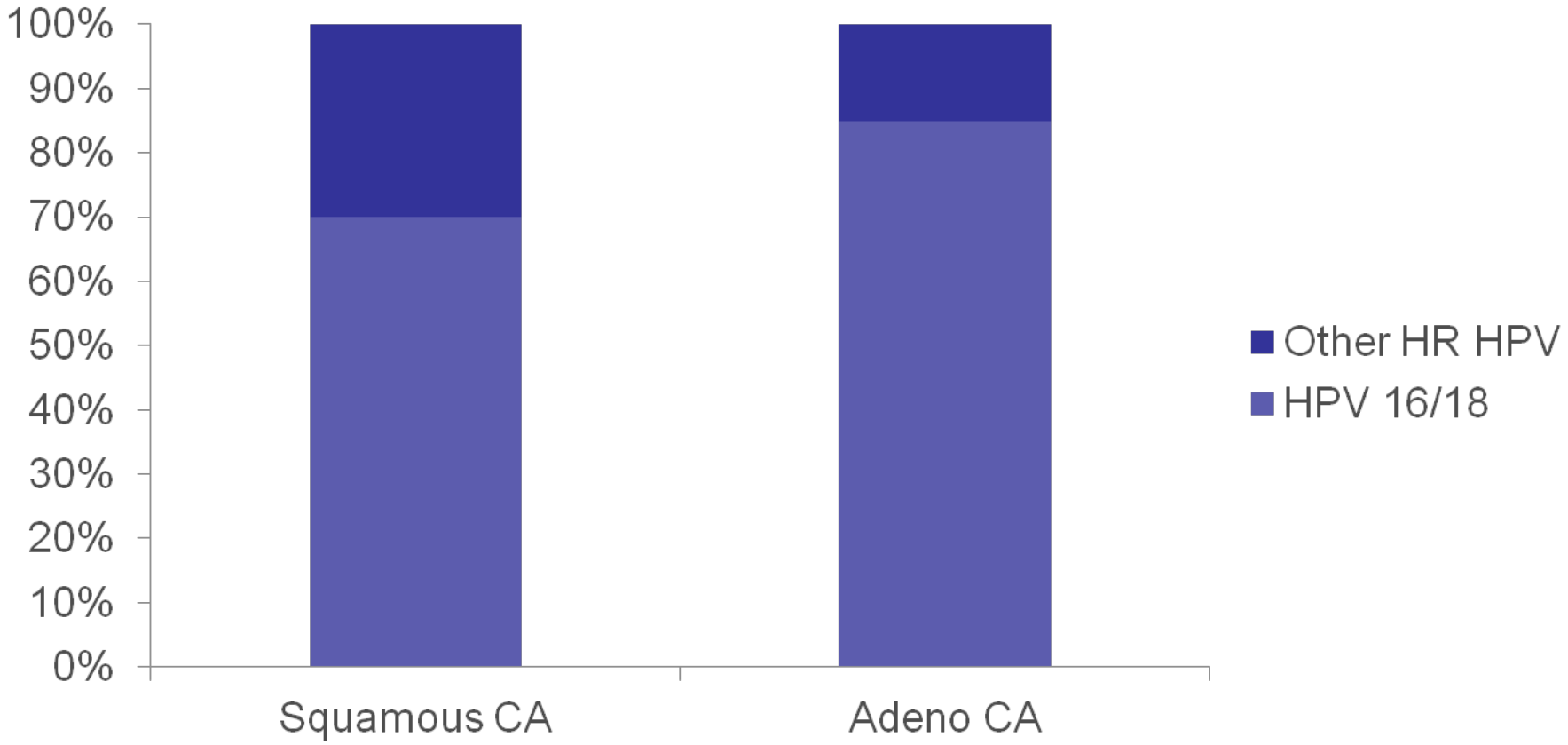
Peto et al Br. J. Cancer 2004:91:942-53

HPV Distribution in Cervical Cancer, CIN3, and Normal Cytology



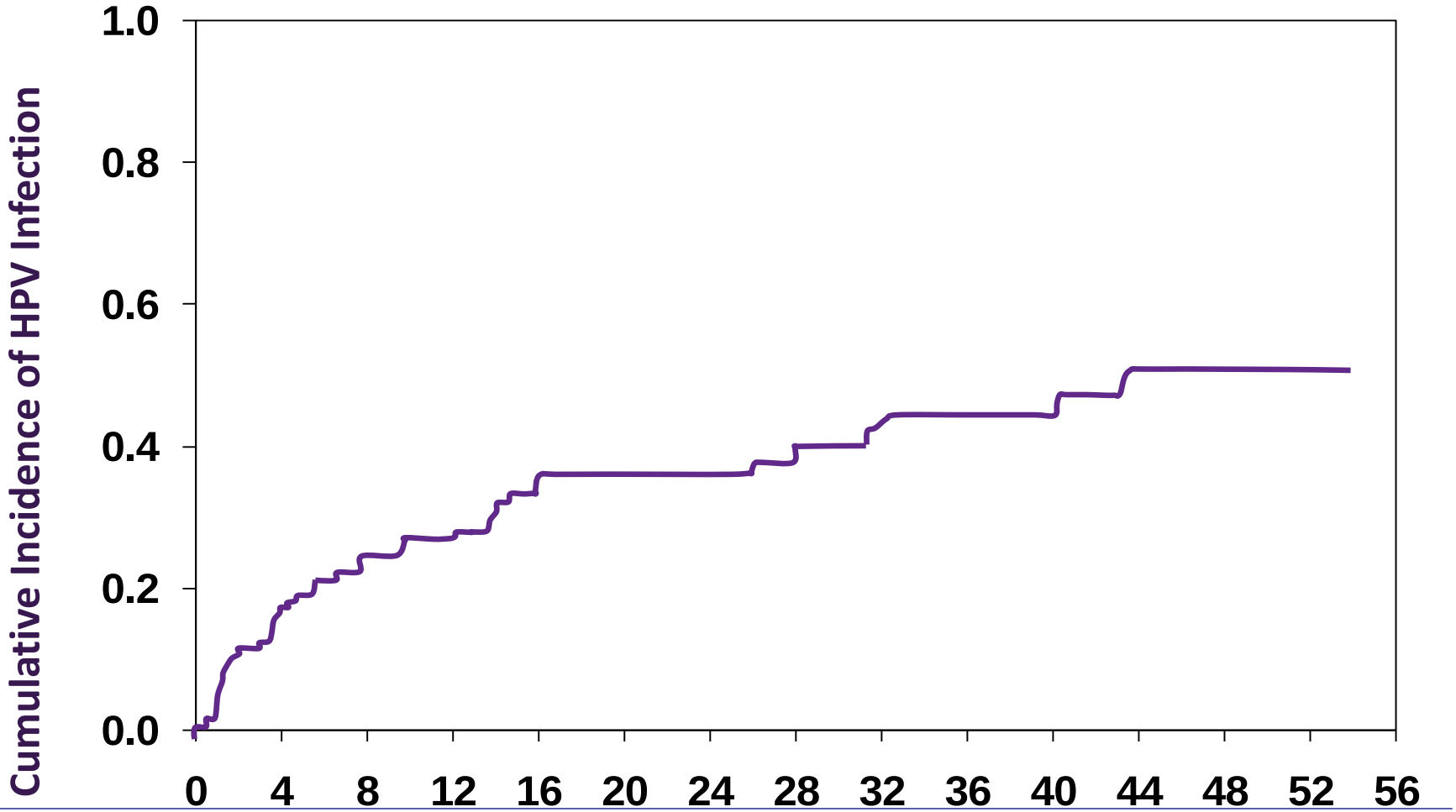
Wheeler CM. JCNCI 2010.

Proportional Impact of HPV 16/18 and Other Viral Types by Tumor Type

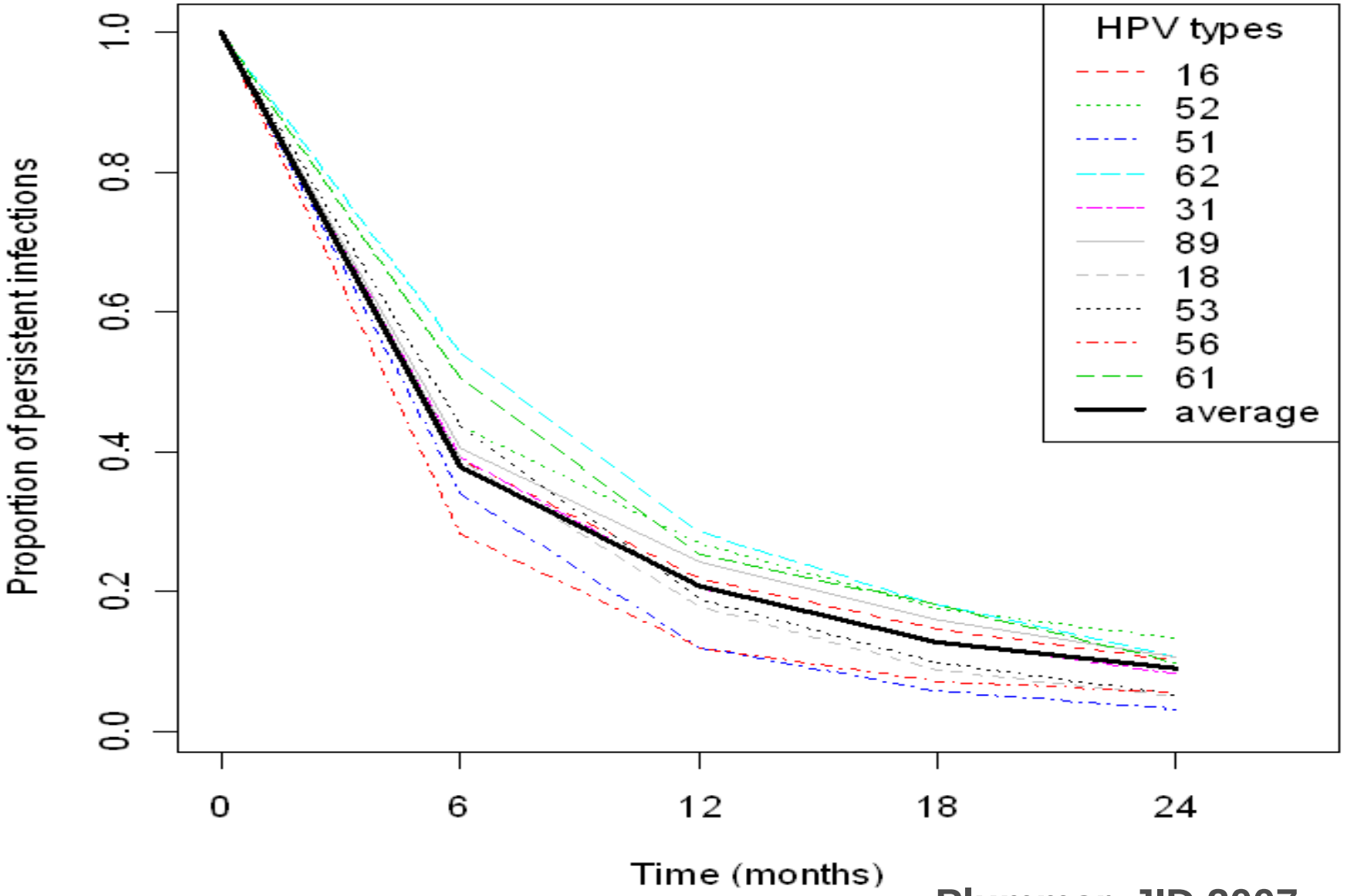


deSanJose. Lancet Oncol 2010

Infection From Time of First Sexual Intercourse (Winer 2003)

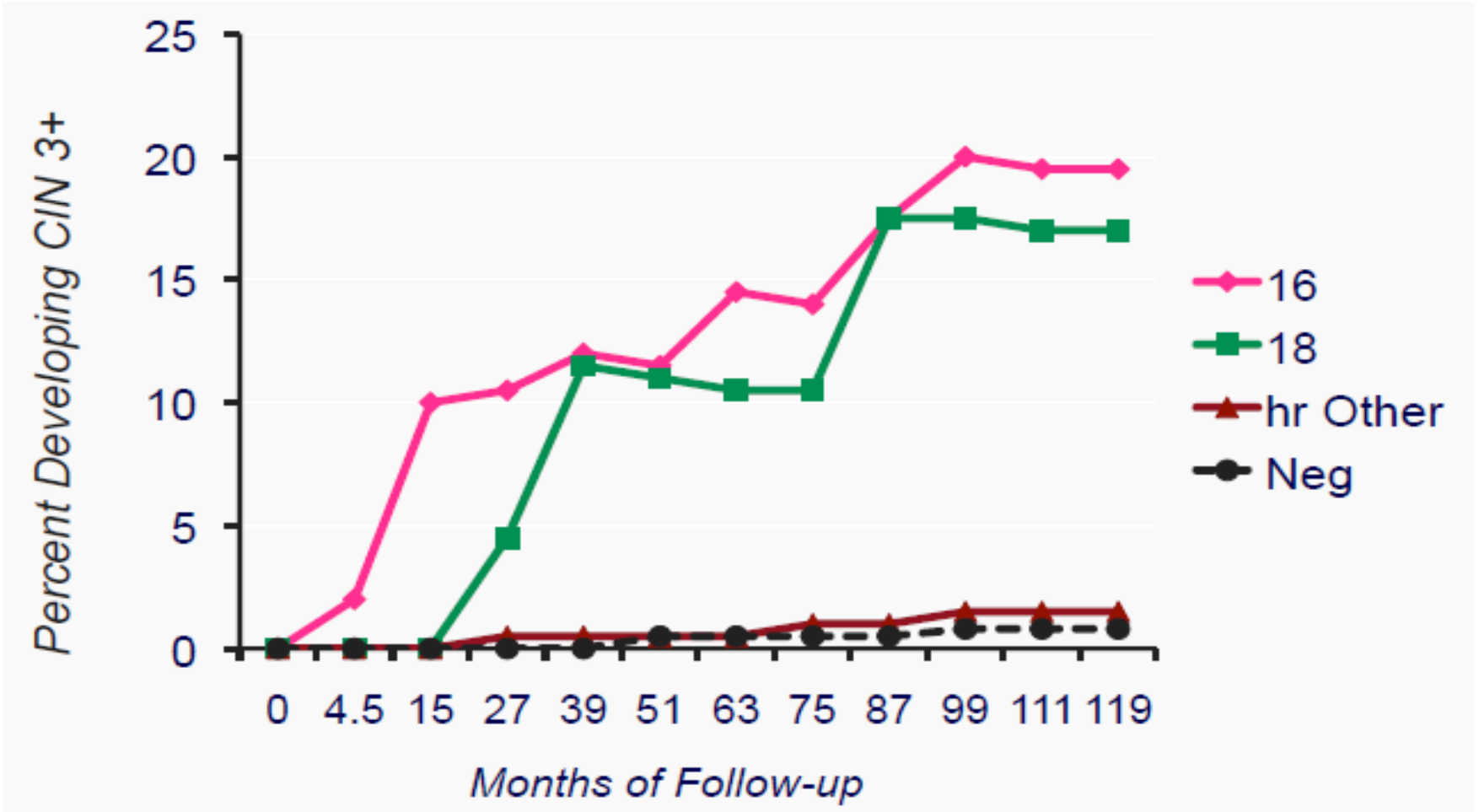


Prevalent HPV Infections Resolve Spontaneously and Rapidly in Young Women



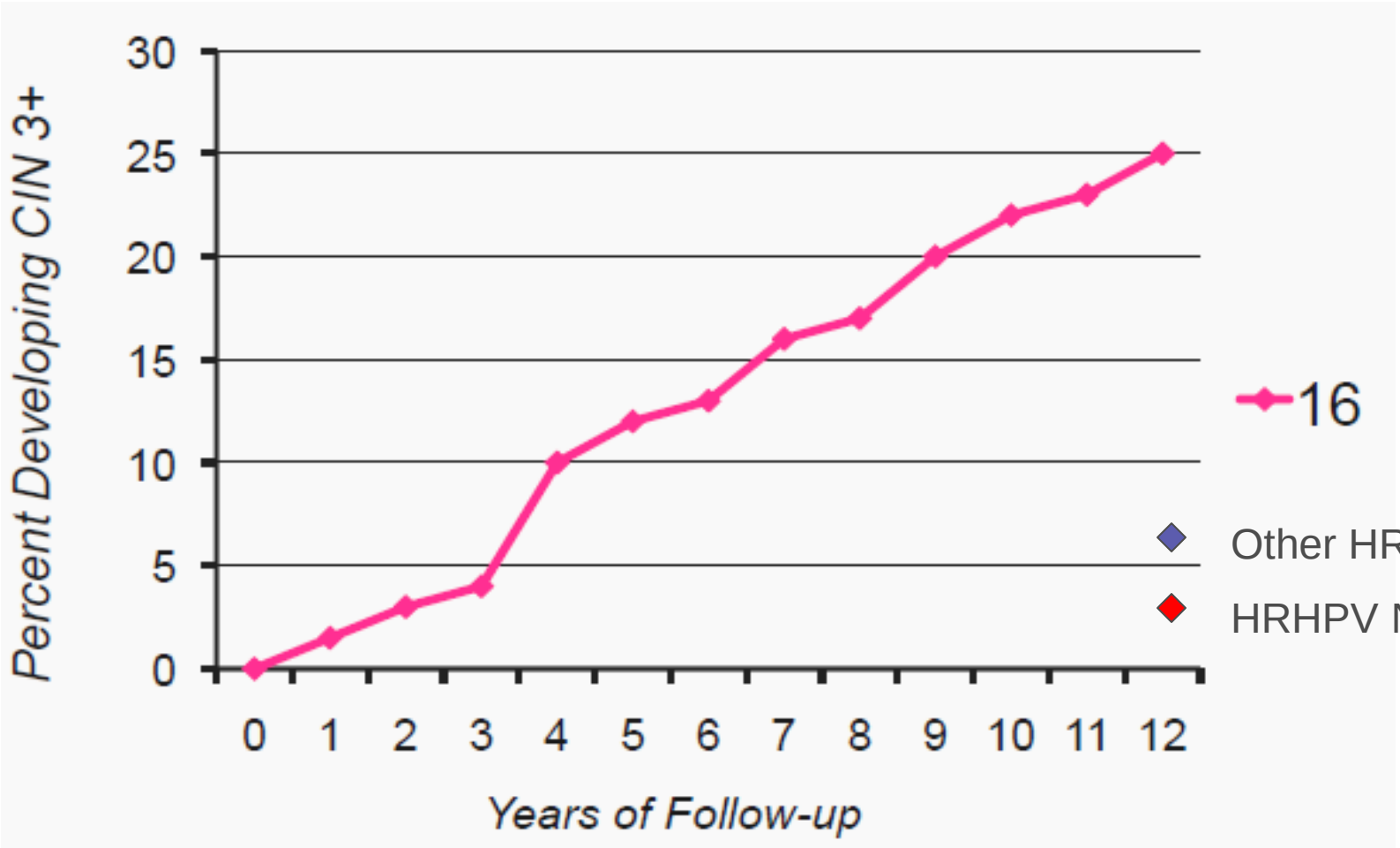
Plummer. JID 2007

Kaiser Portland Study: Risk of CIN3+ in Women ≥30 with NILM Baseline



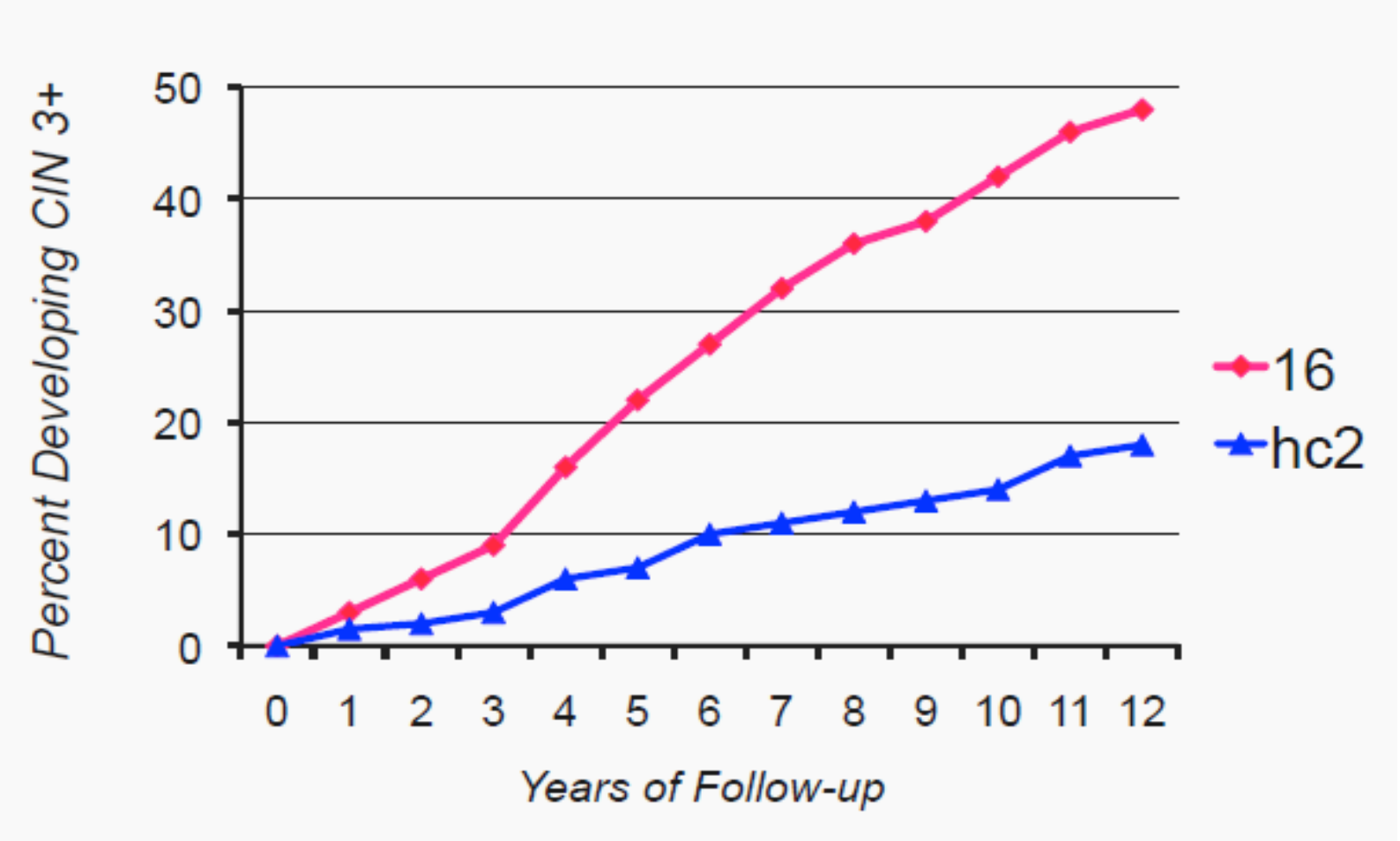
Kahn. JNCI 2005

Danish F/U Study: Long-term CIN 3+ Risk in NILM Cyto by HRHPV Status



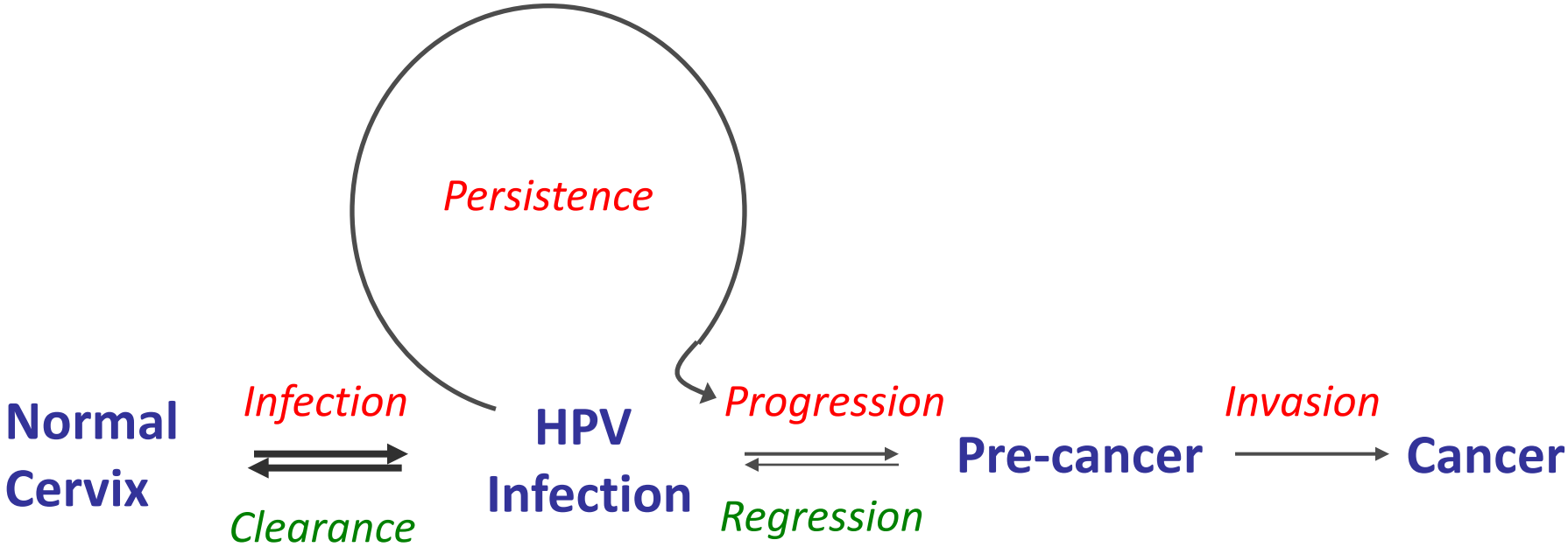
Kjaer. JNCI 2010

Long-term CIN3+ Risk with Persistent HRHPV Infection



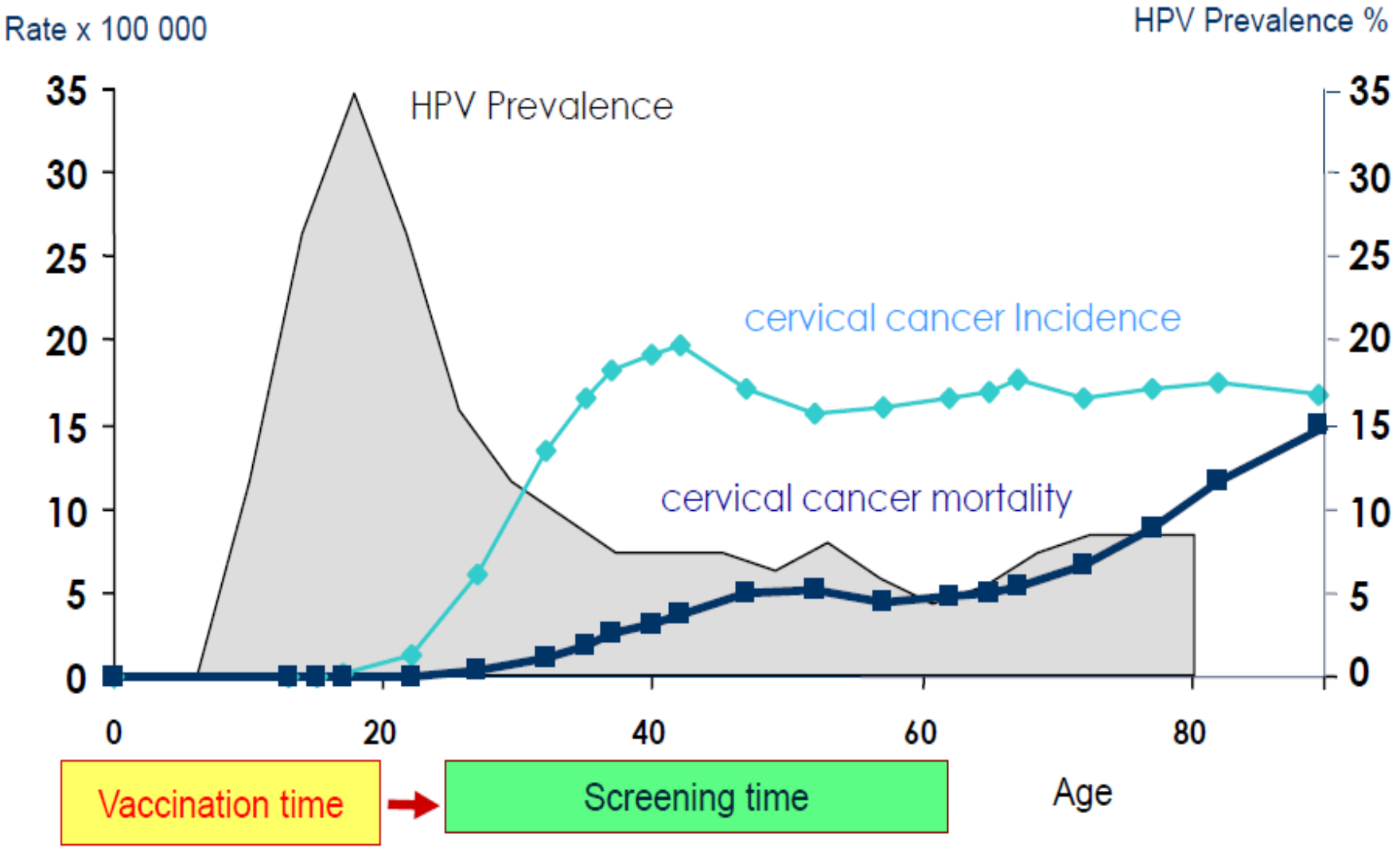
Kjaer. JNCI 2010

Natural History of HPV Infection & Cervical Cancer

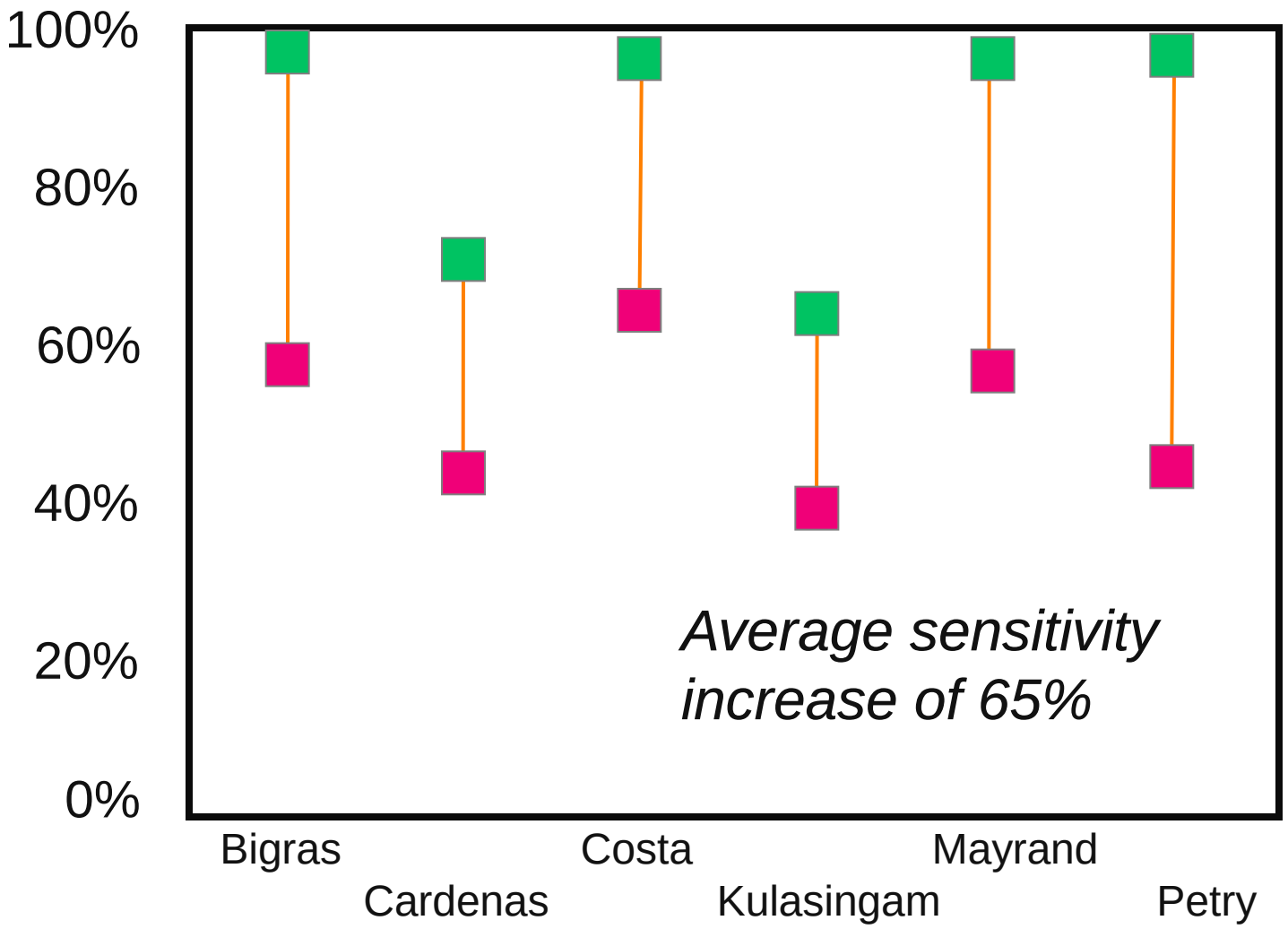


Courtesy of M. Schiffman

HPV INFECTION AND DISEASE PROFILES AMONG WOMEN: DATA FROM FRANCE

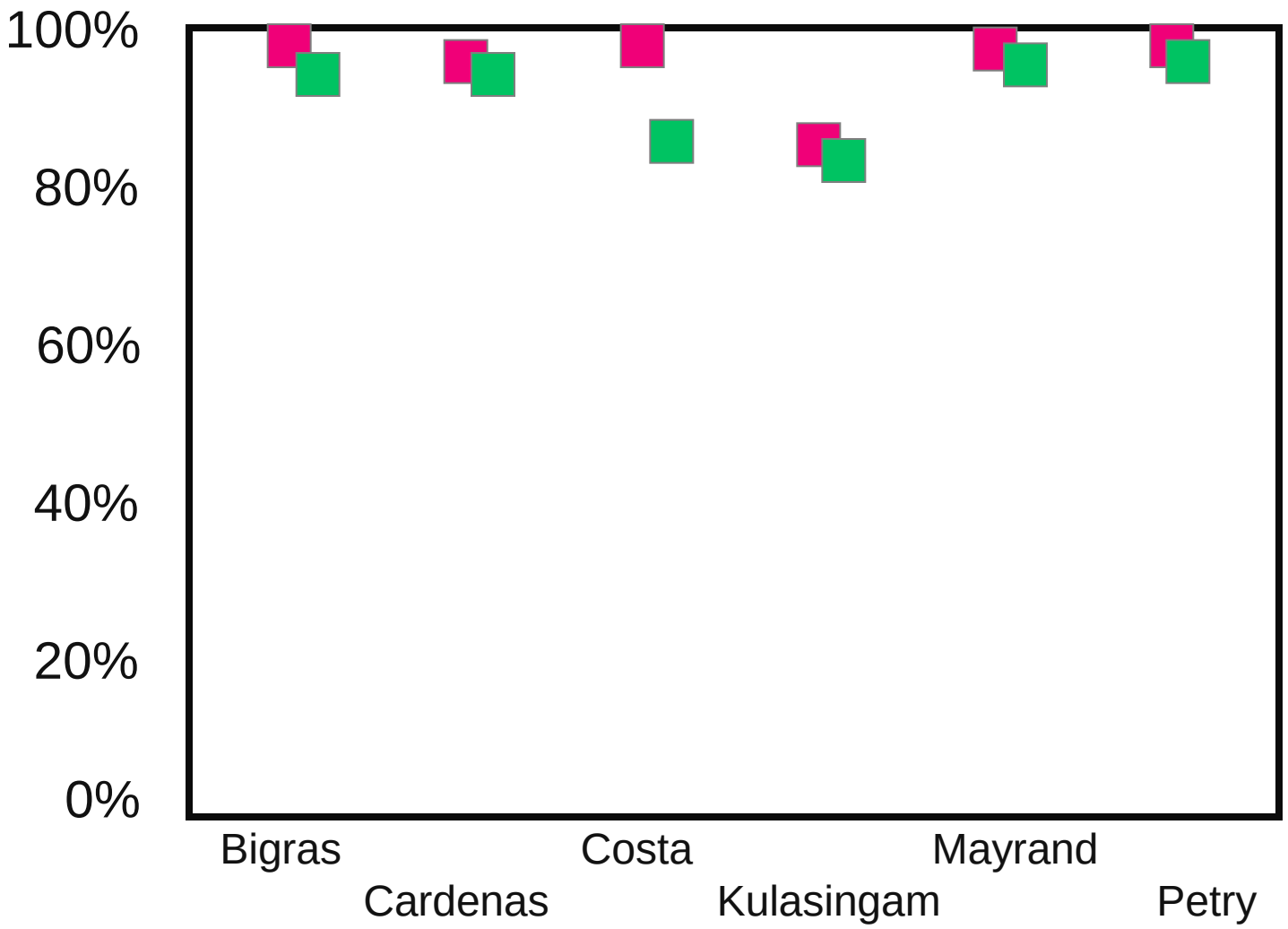


USPTF Review: Sensitivity Pap v HPV for ≥CIN 2



Whitlock Ann Intern Med 2011

USPSTF Review: Specificity Pap v. hrHPV ≥ CIN 2



Whitlock Ann Intern Med 2011

HR HPV Relevance to Screening with Cyto/HPV

- More sensitive and nearly as specific as cyto in ≥ 30 years
- Neg testing identifies women with lower long term risk of developing cancer
- Pos testing may identify earlier smaller volume disease
- Cytology adds additional specificity and predictive value, an HPV neg/NILM cyto has a nearly 0 risk of cancer in 5 years.

Cervical Cancer Screening Guidelines Development Process

- Process jointly convened by ACS, ASCCP, and ASCP between 2009 to 2011
- Assembled expert panel to update/develop new screening recommendations based on a systematic review of evidence
- Process overseen by a Steering Committee, and supported by an independent Data Group.
- 6 topical working groups developed draft recommendations
- Draft recommendations and rationale posted for public comment
- Culminated in a Consensus Conference that finalized the recommendations

2012 ACS/ASCCP/ASCP Cvx Ca Screening Guidelines

<21	No screening
21-29	Cyto alone q 3 years, either liquid or conventional Recommend AGAINST annual cyto
30-65	HPV/cyto "co-testing" combo q 5 years (*preferred*) OR q 3 years cyto alone (*acceptable*) Recommend AGAINST more frequent screening
>65	Discontinue if 3 neg cytos OR 2 neg HPV tests in last 10 years, and most recent screen ≤ 5 years
Post-Hyst	Discontinue if for benign indication
Post Vaccine	Follow age-appropriate recommendations

Follow-up of Discordant Results

HPV neg, ASC-US	Cyto/HPV combo in 5 years (*preferred*) OR Cyto only in 3 years (*acceptable*)
HPV pos, cyto neg	12-month follow-up with cyto/HPV combo OR HPV16 /18 genotype test If pos refer to colpo If neg cyto/HPV at 12-months

Comparison of Guidelines

	ACS-ASCCP-ASCP 2012 ACOG 2012	USPSTF 2012
Age to start	Age 21	Age 21
21-29	Cytology every 3 years (liquid or conventional) Recommend AGAINST annual Pap	Cytology every 3 years (liquid or conventional)
30-65	Cotesting every 5 years (preferred) OR Every 3 years with Pap alone(acceptable) Recommend AGAINST more frequent screening	Cotesting every 5 years OR Every 3 years with Pap alone
>65	Discontinue after 65 if 3 negative Pap tests or 2 negative HPV tests in last 10 years with most recent test in last 5 years	Discontinue after 65 if adequate prior screening
Post-Hyst	Discontinue for benign reason	Discontinue for benign reason
Post HPV Vaccination	Same as unvaccinated	Same as unvaccinated

2011 State of the Evidence for Primary HRHPV Screening

- High-quality evidence suggest superior sensitivity and negative predictive value of primary HRHPV testing.
- Data assessing specificity and relative harms were limited and low quality.
- Data limited to women >30 years, and primarily from studies outside the US.
- May be appropriate for settings with organized screening and referral to specialized centers for evaluation, management, and treatment.
- Those conditions do not apply to most clinical settings in the US.

Primary HPV Screening Studies 2011

In single round screening RCT

- HPV testing is more sensitive for CIN2+ than cyto or HPV/cyto combo
- HPV testing is less specific
- Lack of longer term study limits comparison

In 2 or more rounds RCT

- HPV detects more CIN2+ earlier
- Pap testing detects CIN2+ later but prior to invasion
- No difference in CIN 2+ detection between strategies after 3 rounds (ARTISTIC)

Primary HRHPV Screening Requires Triage, 2011

Colposcopy alone (Ronco 2010)

- Reduction of cervical cancers, but 2x referrals comp to colp
- Sensitivity only 50% in HPV+/cytology negative (Porras 2011)
- Low specificity

Cytology

- High specificity in detecting CIN2+
- Modeling finds it efficient (Myrand 2007)

Molecular/Biomarkers

- Limited studies: cross sectional, small retrospective, archival
- No large scale prospective studies with interval testing

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2013 Primary HPV Screening

- Rijkaart 2012 Netherlands
- Leionen 2012 Finland
- Gyllensten 2012 Germany
- Ogilvie 2012 UK
- Ronco 2013 Italy, Sweden, Netherland, UK

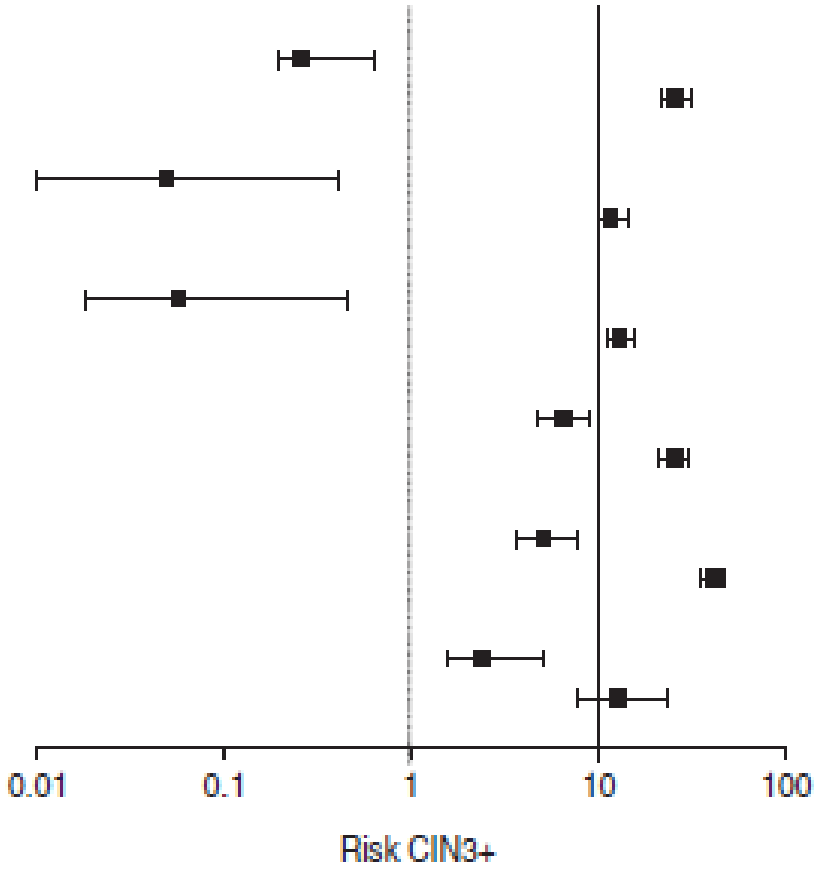
HPV in Population Based Screening, Rijkaart 2012

- Dutch observational cohort study of 25,871 women, 29-61 years
- Compared conventional cyto to HPV PCR
- CIN3+ Risk at 3 years

HPV 16/18 pos	26.1%
HR pos/HPV 16/18 neg	6.6%
Cyto neg	2.4%
HPV neg	0.06%

Cumulative 3-year Risk of CIN3 Rijkaart 2012

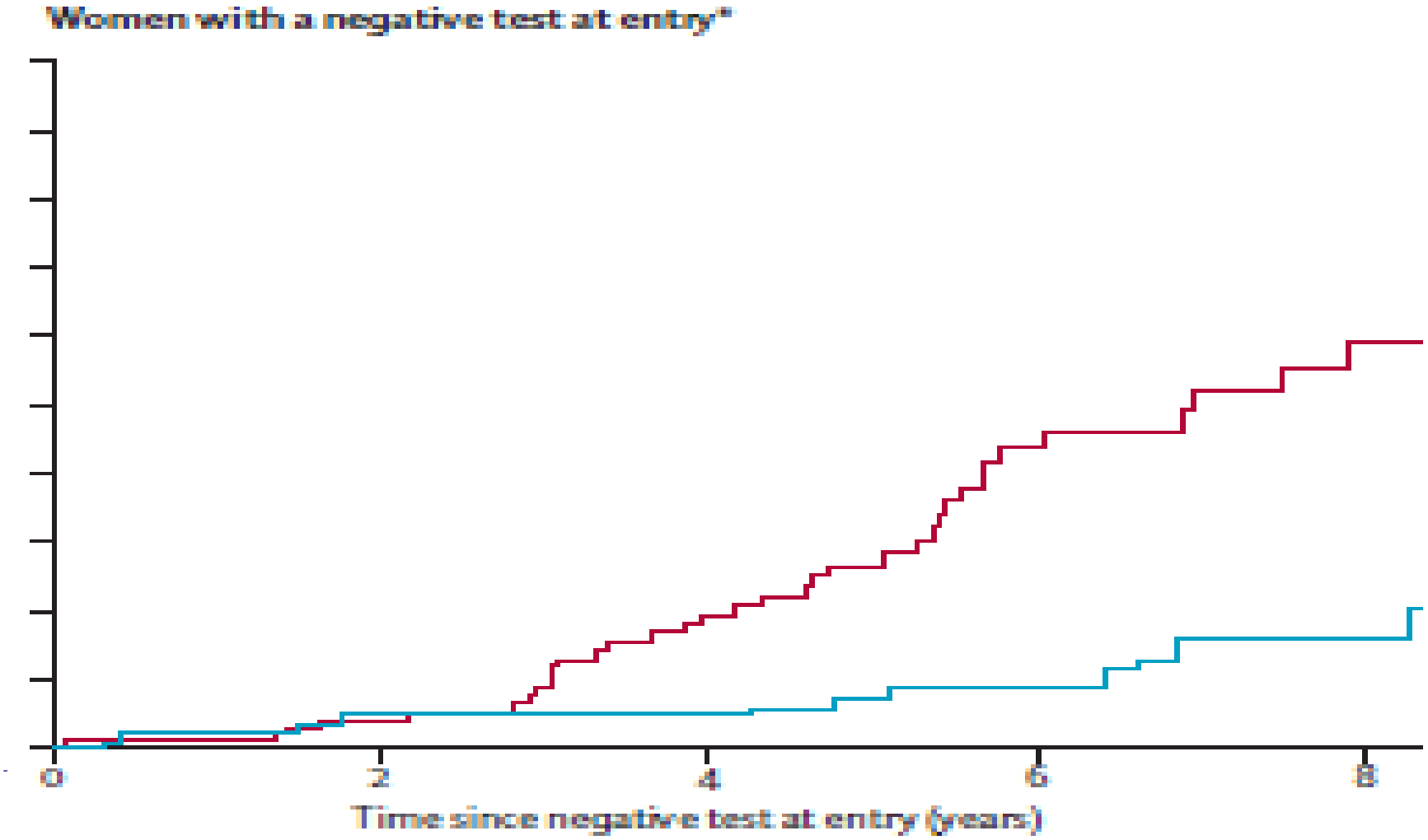
N (% of 25 658)	Screening test	CIN3+ risk % (95% CI)
25 196 (98.2)	Normal cytology	0.26 (0.20–0.65)
462 (1.8)	Abnormal cytology	26.2 (22.5–32.2)
24 175 (94.2)	Normal cytology & hrHPV–	0.05 (0.01–0.42)
1483 (5.8)	Abnormal cytology and/or hrHPV+	11.8 (10.2–14.7)
24 355 (94.9)	hrHPV–	0.06 (0.02–0.46)
1303 (5.1)	hrHPV+	13.2 (11.4–15.9)
881 (3.4)	hrHPV+ & HPV16– and 18–	6.6 (4.8–9.0)
422 (1.6)	hrHPV+ & HPV16+ and/or 18+	26.1 (21.4–31.4)
282 (1.1)	hrHPV+ & normal cytology	5.22 (3.72–7.91)
1021 (4.0)	hrHPV+ & abnormal cytology	42.2 (36.4–48.2)
738 (2.9)	hrHPV+&normal cyto&HPV16– and 18–	2.44 (1.61–5.25)
283 (1.1)	hrHPV+&normal cyto&HPV16+ and/or 18+	13.0 (7.93–23.6)



Efficacy of HPV-based Screening for Cvx CA Prevention, Ronco 2013

- F/U of 176,464, 20-64 years, 4 RCTs of HPV v cyto from Italy, Sweden, UK, Netherlands
- HPV testing with HC2 and PCR
- No difference in detection of invasive ca up to 30 months, after ca increases in cyto arm
- At 6 years after neg screen ca CDR was 50/100k compared to <10/100k in the cyto v. HPV arms
- Improved detection of adenoca

Cumulative Detection of Cervical Cancer in European Screening Trials, Ronco 2013



Outstanding Questions

- Primary HPV screening clearly superior to cytology, but is it better than the HPV/cyto combo?
- Which triage strategy is most efficacious and most cost effective?
- Optimal screening intervals?
- Management of 16/18 neg/ HRHPV pos patient?

Conclusion

- Cervical cancer prevention efforts must balance safety and potential benefit
- New guidelines based on improved understanding of the disease process and limitations of screening
- Policy decisions must be made from a societal perspective, while clinical choices reflect individual preferences and perception of risk
- *Primum non nocere*

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